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Docket No. 2004P-0074
Response to Citizen Petition Filed by Savient Pharmaceuticals

On behalf of a client, these comments are respectfully submitted in opposition to the above referenced Citizen Petition filed February 18, 2004 by Savient Pharmaceuticals Inc. ("Savient"). Savient's Petition requests that FDA take actions that would inappropriately and unnecessarily delay American consumers' access to more affordable generic versions of Savient's Oxandrin® (oxandralone) drug product. As discussed herein, Savient's Citizen Petition is scientifically and legally unfounded, unnecessarily burdens new entrants seeking approval of generic versions of Oxandrin, and is an anticompetitive ruse meant to extend its monopoly on oxandralone drug products. Specifically, Savient is seeking to block approval of competing generic oxandralone products by requesting that the Food and Drug Administration (FDA): (1) scuttle the long-established bioequivalence standards for ANDAs, (2) impermissibly and unnecessarily mandate that ANDA applicants repeat an oxandralone/warfarin drug interaction study based on the unfounded assumption that such studies will show different results than Savient's own previous drug interaction study, (3) require different labeling for generic oxandralone products; (4) impose burdensome and unnecessary CMC standards for generic oxandralone products; and (5) require generic applicants to conduct unnecessary dose proportionality studies for generic oxandralone products. As demonstrated herein, Savient's Petition is without merit and should be denied.

I. BACKGROUND

A. Oxandralone, Warfarin, And Their Drug Interaction Effect

Oxandrin® is an oral oxandralone tablet indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, to promote weight gain in some patients who without definite pathophysiologic reasons fail to gain weight or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of bone pain frequently accompanying osteoporosis. Savient's Petition is based on a well-known drug interaction between oxandralone and the anti-coagulant drug warfarin, whereby coadministration of these drugs causes increased potency of warfarin.

2004P-0074 C1

Warfarin is indicated for prevention of thrombosis and thromboembolic events. Warfarin's pharmacologic effect results from the inhibition of clotting factors and coagulation. The therapeutic effect of warfarin is usually measured in terms of its "international normalized ratio" (INR), a term used to represent an anticoagulant effect. Warfarin's INR range required for therapeutic effects is very close to the level that poses a risk of hemorrhage. Thus, warfarin is considered to be a narrow therapeutic index ("NTI") drug. Warfarin is known to interact with a wide variety of drugs, including oxandralone, and thus the approved warfarin products' labeling specifically warn physicians to continuously monitor prothrombin time ("PT") and INR in patients receiving warfarin and other drugs such as oxandralone for which drug interactions are known.

B. Savient's Drug Interaction Study And Oxandrin Labeling Changes

Oxandrin and warfarin are not approved for combination use, but Savient asserts that Oxandrin is often coadministered with warfarin. *See* Savient Citizen Petition at 6. Specifically, Savient states in its Citizen Petition that approximately 40% of the Oxandrin- using population are patients in long term healthcare facilities, and a significant number of these patients are concomitantly treated with warfarin. *See* Savient Citizen Petition at 7. Savient offers no specific data on the actual scope of concomitant oxandralone/warfarin use. Purportedly to evaluate the oxandralone/warfarin drug interaction, Savient conducted a small bioavailability study involving 15 patients undergoing joint Oxandrin/warfarin treatment, and concluded, not surprisingly, that the concomitant administration of Oxandrin with warfarin significantly increased the anticoagulation effect of warfarin. In response to this study, FDA approved revised labeling for Oxandrin to modify the "precautions" and "drug interactions" sections to read as follows:

Precautions

Concurrent dosing of oxandralone and warfarin may result in unexpectedly large increases in the INR or prothrombin time (PT). When oxandralone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain desirable INR level and diminish the risk of potentially serious bleeding. (See PRECAUTIONS: Drug Interactions) [bold emphasis in original].

* * *

Drug Interactions
Anticoagulants:
Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

Warfarin:
A multi-dose study of oxandralone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-

warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng hr/mL: similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5 fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose) was necessary to maintain a target INR of 1.5. When oxandralone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandralone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

C. Savient's Citizen Petition

Savient latches onto one finding of its drug interaction study to support various requests for FDA action that would block or delay approval of generic oxandralone products. Specifically, the description of the Savient biostudy in the revised Oxandrin labeling reflects that coadministration of either 5 mg or 10 mg of oxandralone BID required a reduction in warfarin dosage of 80-85% in order to maintain a target INR of 1.5. Savient misleadingly characterizes this data as "drug product specific labeling," Petition at 2, 9, 16, and suggests, in various interrelated ways, that this information requires FDA to impose additional requirements and restrictions upon sponsors seeking approval of generic oxandralone drug products. The crux of Savient's Petition is that the reference to the potential need for an 80-85% reduction of warfarin dosing when coadministered with oxandralone is unique and specific to Oxandrin® and that this information cannot be relied upon and used in the labeling for bioequivalent generic oxandralone products. Savient then poses a series of arguments designed to delay or prevent approval of generic oxandralone products. Specifically, Savient requests that FDA:

(1) require generic applicants to conduct their own oxandralone/warfarin drug interaction studies, Petition at 4, 6-9, 17-18;

(2) require generic oxandralone labeling to include the specific results of such requested studies, but also require that generic oxandralone labeling be identical to that of Oxandrin®, Petition at 5, 9-12, 17;

(3) refuse to approve oxandralone ANDAs, and/or deny "AB" ratings to such products, unless the drug interaction studies proposed by Savient demonstrate that the generic oxandralone product produces "identical or nearly identical" results as Savient's Oxandrin study, Petition at 5, 12-13, 18;

(4) require that generic sponsors adopt additional Chemistry, Manufacturing and Controls (CMC) methods, specifications, and procedures, such as specific API particle size requirements and test procedures, Petition at 5, 13-15, 18.

(5) require that generic oxandralone applicants demonstrate dose proportionality between the 2.5 mg and 10 mg dosage strengths of the product, Petition at 5, 15-16, 18.

Savient requests that these actions be taken in the context of new FDA guidance or regulations specifying how the bioequivalence of oxandralone should be established.

II. SEPARATE DRUG INTERACTION STUDIES ARE NEITHER NECESSARY NOR REQUIRED FOR THE APPROVAL AND SAFE USE OF GENERIC OXANDRALONE PRODUCTS

Savient's Petition is premised on the belief that its study established an Oxandrin-specific dosing recommendation for patients receiving both Oxandrin and warfarin, and that generic oxandralone products which meet FDA's established bioequivalence standards could nevertheless have a significantly different effect on the bioavailability of warfarin. Based on this premise, Savient argues that it would be inappropriate for generic oxandralone labeling to include the results of the Savient study. Savient's premises are incorrect for multiple reasons, and as a result, all of the relief requested in the Petition must be denied.

A. Conformity With FDA's Established Bioequivalence Standards Is A Fully Adequate Basis For Approval Of Generic Oxandralone Products

Savient's Petition, at its core, seeks to vitiate FDA's long-established and scientifically sound bioequivalence standards based on a faulty understanding of how bioequivalence is measured and the scientific significance of a product that meets the FDA's mandated 80%-125% confidence intervals for bioequivalence. Specifically, Savient argues that a generic oxandralone product that meets the bioequivalence standard but does so at the lower end (80% range) of the bioequivalence confidence intervals will have a significantly different effect on warfarin bioavailability than either the Oxandrin brand product, or another generic oxandralone product that is at the high end (125% range) of the bioequivalence confidence interval. Specifically, Savient argues that

> the considerable variability in bioavailability permitted by FDA's usual criteria for bioequivalence could result in an oxandralone drug product that has as much as a 20% difference in bioavailability of oxandralone, with a corresponding difference in warfarin anti-coagulation effect. The difference between two ANDA versions of oxandralone in their respective effect on warfarin dose could be even greater (as much as 50%).

Petition at 3. As shown below, Savient's argument is an old myth that was long ago discredited by the scientific community, and because Savient's Petition depends entirely upon this faulty premise, the Petition must be denied.

In response to early brand company arguments that FDA's bioequivalence standards would result in the approval of inequivalent or unsafe generic drugs, the Journal of the American Medical Association (JAMA) published a study conducted by FDA, that examined the actual bioequivalence differences between innovator drugs and generic versions approved between 1984 and 1986. FDA found that under its bioequivalence criteria, the "differences between brand name and generic products actually observed in bioequivalence studies submitted to the agency are small....the FDA has found that the average difference between the observed mean AUCs of the brand name and generic drug products is about 3.5%." Nightingale, S. and Morrison, J., 258 JAMA 9 at 1200, 1202 (Sept. 4, 1987) (copy attached at Tab A). More recently, FDA again conducted a study to evaluate the actual therapeutic equivalence of generic drugs approved under FDA's bioequivalence standards and again found a very close match between branded products and approved generic versions. Based on this review of all generic products approved under bioequivalence studies in 1997, FDA Commissioner Jane Henney reported in JAMA that

> the observed mean difference between the innovator's product and the generic product for AUC (0-t) was +/- 3.47% (SD, 2.84), for AUC (0-inf) it was +/- 3.25% (SD, 2.97), and for Cmax it was +/- 4.29% (SD, 3.72). ... These findings confirm the results of a similar FDA review [cited above] of 224 *in vivo* studies in applications for generic drug products that were approved in 1984 through 1986....Based on these results, practitioners and the public may be assured that **if the FDA declares a generic drug to be therapeutically equivalent** to an innovator drug [using the established bioequivalence criteria], the two products **will provide the same intended clinical effect**."

Henney, J., 282 JAMA 21 (Dec. 1, 1999) (emphasis added) (copy attached at Tab B).

In addition, shortly after the Hatch-Waxman amendments were enacted, FDA held a comprehensive three day public hearing to discuss bioequivalence issues for generic drugs. Of particular significance, Dr. Leslie Benet, President of the American Association of Pharmaceutical Scientists, discussed the very argument raised in Savient's Petition – specifically, the argument that two generic products approved under FDA's bioequivalence standards at the 80% and 120% bioequivalence confidence intervals could exhibit a two-fold change from product to product. As Dr. Benet insightfully and forcefully explained,

> Those who state that there is a potential for a two-fold difference in bioavailability, switching from one generic product to another, are fooling themselves and, more importantly, fooling the public. That is a fallacious statement....To assume that a product would be approved by the FDA that could be 80% different and 120% different is nonsense. That is not feasible.
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> Now, we're fooling the public ... when we make those kinds of statements, and they're not true. That is not the basis of what the regulations state, and I'm

> really surprised that in today's situation in terms of scientific investigation and how we look at data, that those kinds of statements are being made freely and indicating that such a possibility exists. I don't believe it exists.

FDA Bioequivalence Hearing, Statement of Leslie Z. Benet, Ph.D. (October 1, 1986) (emphasis added) (copy attached at Tab C).

As reflected by the FDA's own studies and the analysis of Savient's premise by Dr. Benet, Savient's argument is based on a fundamental misunderstanding of what bioequivalence confidence intervals mean. As a hypothetical, a generic vs brand bioequivalence test in 24 subjects could result in an average bioequivalence ratio between the generic and brand name drug products of 102% (i.e., the generic is equivalent to the brand within +/- 2%) yet the confidence interval could be as wide as from 88% to 112% (or a 24% range). With this understanding of the meaning and significance of the confidence interval, Savient's arguments that different generic oxandralone products could result in up to a 50% difference in blood concentrations is seen for what it is -- in Dr. Benet's words, "fallacious." The fact that FDA's bioequivalence standards employ confidence intervals of 80-125% does not in any way mean that this is the range of blood level differences possible between two generic versions of a product. As seen in the example, and as demonstrated in FDA's two published studies, the average differences in blood concentrations, using the established confidence intervals, are generally less than 5%, and nowhere near the 50% range suggested by Savient.[1]

B. Savient's Study Reflects That The Drug Interaction Between Oxandralone And Warfarin Is Consistent Across A Wide Range Of Therapeutic Doses

Savient's Petition suffers from another fatal flaw, in that it presupposes that even the grossly overstated potential differences in oxandralone bioavailability would have a corresponding effect on warfarin pharmacokinetics. *See* Petition at 11 ("If...a patient switched from an oxandralone drug product that was on the low end of the bioavailability limit to one on the upper end, the level of increased bioavailable oxandralone would increase significantly (up to 50%), and more importantly, there would be a corresponding potentially dangerous increase in the anticoagulation activity of the warfarin."). Significantly, Savient offers no evidence whatsoever that changes in warfarin effects would be correspond in any direct way with the bioavailability of oxandralone at therapeutic oxandralone doses. In fact, Savient's own data, as described in the approved Oxandrin labeling, reflects that the effect of oxandralone on warfarin is similar at both the 10 mg (5 mg BID) and 20 mg (10 mg BID) doses studied by Savient, and thus strongly suggests that the oxandralone effect on warfarin peaks at levels near or below the lowest dose studied (5 mg BID).

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[1] It should also be noted that FDA's confidence interval goalposts are not only used for generic drug products, but may also be used in the approval of innovator drug products. The manufacturer of a brand name drug product would use these goalposts for example, if it needed to determine if the product that it will market is the same as the product that was used in the clinical trials or if a new formulation of an innovator's drug product is the same as the old formulation. FDA would not require, nor, we suspect, would Savient propose, to conduct new oxandralone-warfarin studies every time it modifies the formulation of Oxandrin, even though the same (fallacious) concerns raised by Savient with respect to generic oxandralone products would apply in such situations.

Specifically, Savient's study used either 5 mg or 10 mg of oxandralone (BID), and did not appear to alter the warfarin dose prior to dosing oxandralone based on the oxandralone dose to be administered. Yet despite this **100% difference** in dosage of oxandralone, the *range* of warfarin dose reduction needed was very small -- 80-85% for either 5 mg or 10 mg (BID). Thus, even if a generic oxandralone was subpotent or superpotent (at the 80% or 125% confidence interval range vs Oxandrin), even under Savient's flawed analysis the dose reduction range for warfarin would, at most, change by 1% (20% of the 5% range observed for 5 or 10 mg Oxandrin). This 1% difference (if it exists at all) is hardly a significant safety concern that would justify the regulatory barriers Savient seeks to throw in the path of generic oxandralone applicants.

C. Savient's Study Did Not Establish Specific Dosing Instructions For Warfarin When Co-Administered With Oxandralone

Savient is also far off base in suggesting that its drug interaction studies were product-specific in any way that provides prescribers with meaningful warfarin dose adjustment information. *See* Petition at 2, 9. Although the Oxandrin labeling describes Savient's study and reports that, for either a 5 mg BID or 10 mg BID dose of Oxandrin, an 80%-85% dose reduction for warfarin was required to maintain target INR, this is at best general information that can serve as a starting point for warfarin dose adjustment, subject to further modification based on observed results of individual patient monitoring. Indeed, such ongoing monitoring is required pursuant to both the Oxandrin and warfarin approved labels. *See infra*. The notion suggested by Savient that the 80-85% warfarin dose reduction statement is specific to, and sufficient for the safe use of, Oxandrin®, but not generic oxandralone products, is belied by the fact that the Oxandrin® labeling provides no guidance whatsoever as to recommended warfarin dose reduction differences between patients receiving 5 mg BID and 10 mg BID Oxandrin. If the meaning of the Oxandrin labeling was that patients receiving warfarin and 5 mg BID Oxandrin should receive an 80% warfarin dose reduction, whereas a patient receiving 10 mg BID Oxandrin should have an 85% warfarin dose reduction, then the Oxandrin labeling does not make this clear. Even if this were the case, however, it would further expose the fact, discussed above, that the overall drug interaction potential between oxandralone and warfarin is maximized at an oxandralone dose at or below the lowest therapeutic level, and higher oxandralone dosing does not proportionally or in any significant way magnify the warfarin drug interaction.

Moreover, the Oxandrin® labeling informs prescribers that the average initial warfarin dose in its study was 6.13 mg/day, near the mid-point of the recommended usual warfarin maintenance dose of 2-10 mg/day, but does not disclose the range of initial warfarin doses used in the study, nor any differences in the percentage warfarin reduction required based on the strength of the initial warfarin dose. In other words, the Oxandrin labeling is silent as to whether a high-dose warfarin patient might require only a lesser (e.g., 70%) dose reduction to maintain target INR, or whether a low dose warfarin patient might require a higher percentage dose reduction (e.g., 95%), or vice versa. Given the size and design of Savient's study, it is unlikely that any such differences (which in all probability do not exist) could be detected with statistical significance.

Savient's misleading use of average statistics is also reflected by the fact that its study may well have included subjects receiving a combination of 2 mg warfarin/20 mg oxandralone, and

subjects receiving a combination of 10 mg warfarin/5 mg oxandralone. In either scenario, the labeling implies that an 80%-85% warfarin dose reduction is appropriate. If this implied recommendation is clinically correct, it proves that the alleged differences in generic oxandralone products will have no meaningful clinical differences. If it is incorrect, the Oxandrin labeling is at best incomplete, or at worst, dangerously misleading. In either case, it is clear that the Oxandrin labeling does not provide clinically useful Oxandrin-specific dosing instruction for patients receiving both drugs. Thus, for Savient to suggest that generic oxandralone products should be labeled to reflect the results of duplicative testing to support "careful titration of warfarin" in the name of "safety" is hypocritical and misleading because the Oxandrin® labeling does not provide specific information on how to titrate warfarin across different dosages.

D. The Currently Approved Oxandrin And Warfarin Labeling Fully And Adequately Advises Physicians On How To Address The Oxandralone -Warfarin Drug Interaction For Patients Who Will Receive Generic Oxandralone

Savient argues that generic oxandralone products must have labeling regarding interactions between that specific generic version and warfarin, and that "[f]ailure to include such a precaution for the oxandralone-warfarin drug interaction that includes the specific reduction in warfarin INR is a major safety and bioequivalence issue and renders that ANDA not approvable." *See* Cit. Pet. at 9. Savient further argues that "it is not sufficient for an ANDA to include the exact language and data provided in the Oxandrin labeling, and each ANDA for oxandralone must include data from a clinical study on the interactions of that particular oxandralone drug product and warfarin." *Id.* Savient's argument that generic oxandralone sponsors must conduct their own product-specific drug interaction studies and include those results (as opposed to the results of Savient's study) in generic labeling, is thus put forth in the hope of preventing generic products from complying with the "same labeling" requirement of 21 U.S.C. § 355(j)(2)(A)(v) and 21 C.F.R. § 314.94(a)(8)(iv). As demonstrated above, there is no scientific or legal basis to require generic oxandralone/warfarin studies, nor is there any reason to suspect that the results of such studies would be materially different than the results of Savient's study. However, even if the results of such a hypothetical study would not be "identical" to the results of Savient's study, the use of the Oxandrin® study results in generic oxandralone labeling would not create any safety problem for patients receiving generic oxandralone and warfarin. The physician will need to begin the same dose adjustment process regardless of whether the patient is prescribed Oxandrin or generic oxandralone. Thus, the use of the Oxandrin drug interaction labeling for generic oxandralone products is legally and medically justified, and must be permitted by FDA.

The inherent safety of using the results of the Oxandrin study in the labeling of generic oxandralone products is demonstrated in part because, as shown above, the Oxandrin labeling does not provide specific reliable warfarin dosing instructions. In addition, the safety of generic products using the Oxandrin drug interaction information will be assured because the dosing instructions and precautions in both oxandralone and warfarin labeling emphatically require careful and continuous monitoring of patients' INR scores and warfarin dose adjustments as necessary. Thus, no competent physician would ever simply provide an 80-85% warfarin dose reduction and fail to follow up with ongoing INR monitoring and further dose adjustments.

At present there are four approved prescription drug versions of warfarin: Coumadin® which has marketed since 1956; and generic warfarin sodium products marketed by Barr Laboratories, Inc., Sandoz, Inc., Taro Pharmaceuticals, Inc., and USL Pharma.[2] The labeling of all warfarin drug products provide adequate information on the potential interactions of warfarin with other drugs, and also provide adequate instructions to physicians on how to administer warfarin when coadministered with drugs with which warfarin exhibits drug-drug interactions. Specifically, the warfarin labels provide the following relevant information.

- The "precautions" sections list potential drug interactions with various steroids, including 17-alkyl testosterone derivatives, of which oxandralone is a well-known example. Other steroids, such as adrenocortical steroids, are also listed.

- The "Warnings" and "Precautions" sections of the labeling alert physicians that warfarin treatment must be highly individualized. Specifically, the "warnings" section of the warfarin labeling states that:

  "It cannot be emphasized too strongly that treatment of each patient is a ***highly individual matter***...Dosage should be controlled by ***periodic determinations*** of PT/INR or other suitable coagulation tests." (Emphasis added).

- In addition, the Precautions section reiterates this by boldly emphasizing that

  "Periodic determination of PT/INR or other suitable coagulation test is essential....It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including botanicals, are initiated, discontinued or taken irregularly."

- Moreover, the warfarin Precautions section concludes by stating:

  "Because a patient may be exposed to a combination of the above factors [including drug interactions], the net effect of Coumadin [warfarin] on PT/INR response may be unpredictable. ***More frequent PT/INR monitoring is therefore advisable.***" (Emphasis added).

In addition, other parts of the Oxandrin labeling (unrelated to Savient's study) also emphasize the need for caution when oxandralone is dosed with warfarin. Specifically, the Oxandrin label states:

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[2] Significantly, all generic warfarin products available in the market today were found to be bioequivalent and therapeutically equivalent to Coumadin® under FDA's standard bioequivalence criteria and thus have received "AB" ratings.

- "Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. ***Patients receiving oral anticoagulant therapy require close monitoring***, especially when anabolic steroids are started or stopped." (Emphasis added).

- "When oxandralone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandralone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding."

That treatment with warfarin is a highly individualized one is a critical fact overlooked by Savient in its citizen petition. Thus, in evaluating whether generic oxandralone products will be safe when used concomitantly with warfarin, it is inappropriate to assume, as Savient does, that prescribers will rely solely (or at all) upon the oxandralone labeling's general discussion of Savient's drug interaction study, and ignore the numerous other references in both products' labeling to the need for ongoing individualized dose monitoring. Rather, prescribers must, and will, follow the numerous warnings and precautions in warfarin labeling which clearly and emphatically instruct physicians to conduct frequent PT/INR monitoring when patients are also administered potentially interacting drugs such as oxandralone. Thus, identicality of generic oxandralone labeling to the existing Oxandrin labeling will adequately address all safety and effectiveness concerns related to the coadministration of oxandralone with warfarin without having to resort to additional clinical trials by the generic applicant.

III. SPECIFIC CMC REQUIREMENTS, AND DOSE PROPORTIONALITY STUDIES, ARE UNNECESSARY FOR GENERIC OXANDRALONE PRODUCTS

Savient claims in its citizen petition that oxandralone represents a drug with actual or potential bioequivalence problems based on certain physicochemical properties of oxandralone which allegedly correspond to criteria identified in 21 C.F.R. § 320.33(e). Petition at 13-15, 17. The properties identified by Savient include low solubility, slow dissolution rate, polymorphic physical properties, potential dependence of bioavailability on particle size, and a high ratio of excipients to active ingredients. Based on these criteria, Savient argues that "these characteristics will render oxandralone drug products not bioequivalent, and therefore not AB therapeutically equivalent, . . . further . . . [illustrating] the need for drug specific warfarin interaction data in each oxandralone drug product labeling," and that "all oxandralone applications must have additional Chemistry, Manufacturing and Controls [CMC]. . . ." *See* Petition at 5, 17-18. Savient further argues that the alleged bioproblem properties of oxandralone require that generic applicants specifically establish dose proportionality between different strengths of their oxandralone products. Savient's arguments here are also misplaced.

First, the regulation Savient relies upon applies only with respect to drug products that are not subject to the ANDA provisions of the statute. *See* 21 C.F.R. § 320.32 (allowing FDA to establish bioequivalence standards, based on criteria set forth in section 320.33, "for a product not subject to section 505(j)"). *See also,* 21 C.F.R. § 320.22(c) (FDA may waive the *in vivo* bioequivalence requirement for DESI-effective drugs (not subject to an approved NDA or ANDA) unless the drug is a bio-problem drug pursuant to section 320.33). For drug products such as oxandralone that *are* subject to section 505(j), FDA's established bioequivalence standards apply regardless of the physicochemical properties alleged by Savient.

Second, even if it were the case that the properties alleged by Savient could affect bioequivalence of generic oxandralone products (a theory for which Savient provides no documentation at all), established bioequivalence studies and standards are fully adequate to detect the effect of such differences. Thus, if a generic applicant's product displays physicochemical differences from Oxandrin and such differences actually affect bioavailability or bioequivalence, the product will not pass the biostudy. If a generic drug product does pass a standard biostudy, it would prove that any physicochemical differences do not matter. Either way, Savient's Petition does not require, allow, or even support, the imposition of any specific CMC or heightened bioequivalence standard for generic oxandralone products.

Finally, Savient's argument that the alleged bioequivalence problems of oxandralone require dose proportionality studies of generic oxandralone products is without support or merit. Savient merely refers to its arguments regarding the physicochemical properties of oxandralone and hypothesizes that a 2.5 mg dosage strength could have radically different bioavailability than a 10 mg dose of the same formulation. Petition at 16. Yet Savient offers no basis for *why* oxandralone's properties would even potentially result in such disparities. In fact, there is no basis for Savient's wild speculation. Moreover, Savient incorporates its fallacious argument that different generic oxandralone products whose bioequivalence confidence intervals vary would not be truly bioequivalent, and would have an effect of warfarin dosing. For the reasons discussed in section II, *supra*, Savient's CMC and dose proportionality arguments must also be rejected as baseless.

IV. CONCLUSION

As demonstrated herein, there is simply no merit to any of Savient's arguments. Rather, Savient's Petition is a desperate, baseless, anticompetitive attempt to thwart or delay generic competition for perhaps its most valuable product. Savient's perceived need to engage in such tactics is better understood in light of the fact that the company apparently is in desperate financial trouble. Savient was in discussions to be acquired by generic drug giant Teva Pharmaceuticals, but that merger was called off in late 2003 because, in the view of at least one analyst, Teva "discovered either that there was nothing to acquire, or that it would be very difficult to solve the conundrum that goes by the name of management at Savient." *See* Globes Online, *Unwanted by Teva, Savient Plunges*, May 18, 2004 (available at www.globes.co.il/DocsEn/did=797593.htm). Indeed, shortly after the failed acquisition by Teva, Savient's longtime Chairman Sim Fass announced his retirement,

and the company's stock began "rising on the news of his resignation." Globes Online, *Savient Into The Unknown*, May 27, 2004 (available at http://www.globes.co.il/DocsEn/did=800019.htm). This article also noted that "[t]he unexplained at Savient far exceeds the explained. The company's flagship drug faces an uncertain future, and not much is known about Christopher Clement, the new CEO.... The share responded positively, but future developments must be awaited."

FDA should, and must, continue to apply its longstanding and well supported bioequivalence standards and procedures in evaluating generic oxandralone applications, and not allow frivolous Petitions such as Savient's to detract from the Agency's important mission to review and approve bioequivalent generic drugs in the most timely manner possible. Savient's petition should and must be denied.

Respectfully submitted,

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